

PATENT COOPERATION TREATY

PCT

REC'D 23 JUL 2004

INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 03200511	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US03/32597	International filing date (day/month/year) 16 October 2003 (16.10.2003)	Priority date (day/month/year) 18 October 2002 (18.10.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/56, 31/565 and US Cl.: 514/177, 178, 179 169		
Applicant UNIMED PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 14 May 2004 (14.05.2004)	Date of completion of this report 08 July 2004 (08.07.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer <i>Sreeni Padmanabhan</i> Sreeni Padmanabhan Telephone No. 703.308.0198

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/32597

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-35 _____ as originally filed
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.
- ☒ the claims:
pages 36-42 _____, as originally filed
pages NONE _____, as amended (together with any statement) under Article 19
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.
- ☒ the drawings:
pages NONE _____, as originally filed
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.
- ☐ the sequence listing part of the description:
pages NONE _____, as originally filed
pages NONE _____, filed with the demand
pages NONE _____, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/32597**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-48</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-48</u>	NO
Industrial Applicability (IA)	Claims <u>1-48</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Please See Continuation Sheet

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1-48 meet the criteria of PCT Article 33(2) because the prior art does not teach the employment of the composition herein in the claimed method of improving sexual performance in a male subject.

Claims 1-48 lack an inventive step under PCT Article 33(3) as being obvious over Omar (5,730,987) and Mak et al. (WO 99/24041) in view of Allen (WO 96/227372) and Heiber et al. (WO 93/25168).

Omar discloses that the particular steroid, testosterone and yohimbine or papaverin in a combination to be administered are useful in the composition and the method of the treatment of impotent in human males, i.e., erectile dysfunction. See col.1 lines 17-65 and claims 6-8.

Mak et al. discloses an enhancement of the penetration of transdermally (percutaneously) or topically applied a pharmaceutical composition comprising an active agent, testosterone, and a penetration-enhancing system that comprises oleic acid (a fatty acid having 17 carbon atoms), C1-C4 alcohol (e.g., ethanol, 2-propanol), and the gelling agent (a thickener), CARBOPOL (a polyacrylic acid). See abstract, page 3 lines 1-5, page 10 Example 1, and Figure 2.

Heiber et al. (WO 93/25168) discloses that testosterone compositions comprising a transdermal (percutaneous) delivery system comprising C2 or C3 alcohol, a penetration enhancer therein, i.e., glycerine, and a gelling agent, are useful in methods moderating and maintaining transdermal drug delivery to the derma at a relatively sustained rate over the duration of application to situs. See abstract, Example 3 at page 19-21, and claims 1-46 and 48.

Allen (WO 96/227372) discloses a topical cream composition useful for treating male erectile dysfunction comprising the particular penetration enhancer, isopropyl myristate or glycerine. See abstract and claim 1 and 4.

One having ordinary skill in the art would have been motivated to employ the particular steroid, testosterone, C1-C4 alcohol, and the particular penetration enhancer, C8-C22 fatty acid and isopropyl myristate in a method for improving the efficacy of the composition herein useful for treating erectile dysfunction in an eugonadal male since the composition containing testosterone of Mak et al. is known to be useful in a method for improving the efficacy of percutaneously delivering a pharmaceutical because this composition further comprises a transdermally or topically penetration-enhancing system encompassing an oleic acid (a fatty acid having 17 carbon atoms), C1-C4 alcohol (e.g., ethanol, 2-propanol), and a penetration enhancer and a gelling agent. Moreover, the teachings of Heiber et al. have further provided the motivation to make the present invention since testosterone compositions of Heiber are known to comprise a transdermal (percutaneous) delivery system comprising C2 or C3 alcohol, a penetration enhancer therein, i.e., glycerine, and a gelling agent, and these compositions are known to be useful in methods moderating and maintaining transdermal drug delivery to the derma at a relatively sustained rate over the duration of application to skins.

Therefore, one of ordinary skill in the art would have found it obvious to employ the composition of Mak et al. in the instant claimed method. The topical cream composition of Allen is also known to be useful for treating male erectile dysfunction or improving sexual performance comprising the particular penetration enhancer herein, isopropyl myristate, which provides additional motivation for the claimed method. Thus, the motivation to employ known drug delivery systems to enhance the penetration of actives herein transdermally (percutaneously) or topically for treating male erectile dysfunction is clearly provided by the Mak et al. and

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Allen references.

Further, the particular steroid, testosterone, is well known to be useful to treat erectile dysfunction or improving sexual performance in a male according to Omar. Moreover, all another pharmaceutical employed in the combination with testosterone recited in claims are well known in the art to be useful in treating erectile dysfunction or improving sexual performance in a male.

Therefore, one of ordinary skill in the art would have reasonably expected that adding another pharmaceutical useful for treating erectile dysfunction such as sildenafil to Mak's composition would improve the therapeutic effect of Mak's composition to treat male erectile dysfunction or improving sexual performance.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts of active ingredients in the composition because the optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

Claims 1-48 meet the criteria of PCT Article 33(4) because the claimed method of improving sexual performance in a male subject has industrial applicability in the pharmaceutical art.

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NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No. PCT/US03/32597	Applicant's or agent's file reference 03200511	Date of informal communication (day/month/year) 26 June 2004 (26.06.2004)
Applicant UNIMED PHARMACEUTICALS, INC.		

<u>Communication</u> <input checked="" type="checkbox"/> by telephone <input type="checkbox"/> personal	<table style="width: 100%;"> <tr> <td style="width: 50%;"><u>Participants</u></td> <td style="width: 50%;"> <input type="checkbox"/> Identity checked <input checked="" type="checkbox"/> authorization checked <input type="checkbox"/> personally known </td> </tr> <tr> <td><input checked="" type="checkbox"/> Applicant: UNIMED PHARMACEUTICALS, INC.</td> <td></td> </tr> <tr> <td><input checked="" type="checkbox"/> Agent: Amanda T. Barry</td> <td></td> </tr> <tr> <td><input checked="" type="checkbox"/> Examiner(s): Shaojia A. Jiang</td> <td></td> </tr> </table>	<u>Participants</u>	<input type="checkbox"/> Identity checked <input checked="" type="checkbox"/> authorization checked <input type="checkbox"/> personally known	<input checked="" type="checkbox"/> Applicant: UNIMED PHARMACEUTICALS, INC.		<input checked="" type="checkbox"/> Agent: Amanda T. Barry		<input checked="" type="checkbox"/> Examiner(s): Shaojia A. Jiang	
<u>Participants</u>	<input type="checkbox"/> Identity checked <input checked="" type="checkbox"/> authorization checked <input type="checkbox"/> personally known								
<input checked="" type="checkbox"/> Applicant: UNIMED PHARMACEUTICALS, INC.									
<input checked="" type="checkbox"/> Agent: Amanda T. Barry									
<input checked="" type="checkbox"/> Examiner(s): Shaojia A. Jiang									

Summary of communication:

Upon request by the examiner, applicant's representative Amanda T. Barry agreed to proceed to the 409 the International Preliminary Examination Report, directly in order to meet the administrative deadlines for the instant application and/or expedite the PCT process.

☐ An extension of time limit is granted (Form PCT/IPEA/427).

☒ A copy of this note is being sent to the applicant with Form PCT/IPEA/429.

PCT/IPEA/424.

Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	<table style="width: 100%;"> <tr> <td style="width: 50%;"> Authorized officer Sreen Padmanabhan </td> <td style="width: 50%;"> Telephone No. 703.308.0198 </td> </tr> </table>	Authorized officer Sreen Padmanabhan	 Telephone No. 703.308.0198
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Form PCT/IPEA/428 (July 1992)